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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,459	05/02/2005	Curtis C. Harris	63139(47992)	3076

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,459	HARRIS ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-28 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28 and 32* is/are rejected.

7)☒ Claim(s) *21-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 20-28 and 32 are pending in the application.

This Office Action is in response to the Amendment filed on 6/16/2010.

Response to Amendment

The rejection of claims 20-28 under 35 U.S.C.102 (e) has been withdrawn in light of the Amendment.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-28 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claims are drawn to a microarray comprising a solid support and a sufficient number of genes, or polynucleotide fragments or RNA transcripts thereof, that are differentially expressed in a small cell lung cancer cell (SCLC), a large cell neuroendocrine carcinoma neuroendocrine tumor cell (LCNEC), a typical carcinoid neuroendocrine tumor cell (TC) or an atypical carcinoid neuroendocrine tumor cell (AC), relative to a normal or a cell belong to a different neuroendocrine tumor cell type, to permit said microarray to distinguish a neuroendocrine tumor cell, and wherein said genes, or polynucleotide fragments or RNA transcripts thereof consists of CPE and GGH, or a polynucleotide fragment or RNA transcript thereof.

The breadth of the scope:

The breadth of the scope is broad. Claim 20 encompasses any of the fragments or RNA transcripts of CPE and GGH for the purpose of distinguishing between any type of neuroendocrine tumor cell.

The teaching of the specification and the presence of working examples:

The specification discloses an example of isolating mRNA from 17 pulmonary neuroendocrine tumor (NET) (11 TC, 2 LCNEC, 3 SCLC and 1 combined SCLC and LCNEC) and for microarray analysis. The specification teaches 198 genes are identified that clustered the 17 tumors into groups in agreement with morphological classification (see page 60). In Table 6, CPE is identified in cluster 1, and GGH is in cluster 2, and the expression ratio data indicate that

CPE is overexpressed in TC, whereas GGH is overexpressed in LCNEC (see Figure 3, and Table 7). The specification also disclose that in verification experiment by quantitative RT-PCT, CPE is elevated in 8/11 TC, however, GGH is not verified by this method (see Figure 5). The specification further discloses that protein expression of CPE and GGH are analyzed by immunostaining using 68 available pulmonary NET samples and generated 55 informative data. The specification teaches that no signal is detected in bronchial epithelial cells or pneumocytes of normal lung, whereas some strong positive staining is detected in scattered neuroendocrine cells of terminal bronchiolar epithelia and in some macrophages. TC display a positive stain, LCNEC has weak stain, and SCLC is completely negative. The specification also discloses that normal lung and TC display a negative stain for GGH, whereas LCNEC and SCLC display positive staining (see page 67-68). Table 8 summarizes that result of this study wherein CPE is positive in majority of TC and AC, whereas GGH is positive in majority of SCLC and LCNEC. However, the specification indicate that the GGH stain for TC, CPE stain for AC and LCNEC are not statistically significant (see page 68, lines 8-16). The specification also disclose that GGH gene is regulated at both transcriptional and translational levels, wherein LCNEC cells the mRNA and protein are consistently elevated, whereas SCLC cases, the mRNA elevation is not detected by microarrays (see page 72, lines 18-23).

The above teaching is not sufficient for enable the claimed microarray consisting only two genes or fragments of said genes, CPE and GGH, for the purpose of distinguishing between NET cells. Although said genes appears to be differentially expressed in TC, AC, LCNEC, SCLC, some of the difference is not statistically significant, thus no conclusion can be made with regard to the combination of expression at mRNA level for such genes. In other words, one of

skill in the art cannot identify the sample as LCNEC, SCLC, AC or TC based on the expression of CPE or GGH relying on the teaching of the specification. For example, if a tumor sample has a high expression of CPE relative to normal tissue, whether it is TC, AC, LCNEC or SCLC is unpredictable because all of such NET could have CPE expression according to the data presented in Table 8. Moreover, the specification fails to teach which part or fragment of the genes, can serve as a marker to identify NET. Therefore, the claimed invention is unpredictable based on the teaching of the specification.

The state of prior art and the level of predictability in the art:

The state of art at the time of filing recognizes that NETs constitute a heterogeneous group of neoplasm that may arise in virtually every topographic localization in the body as a consequence of malignant transformation in the body. NETs can further be subclassified into TC, AC, SCLC and LCNEC for thymic endocrine cells and bronchopulmonary endocrine cells (see Hofsli, Pituitary, 2006. Vol. 9, pages 165-178, page 166, Figure 1). Despite the breakthrough of establishing high throughput gene analysis microarray techniques which contributes to be a valuable tool in the subclassification of tumors, researchers also find that human proteome is much more complex than previously recognized, and absolute correlation between the mRNA expression level and the corresponding protein level is rather unpredictable (see page 178, 1st col., 1st paragraph). The prior art is silent whether a microarray consisting CPE and GGH polynucleotides, or fragments thereof, may be used to distinguish between all NETs. In the Hofsli article, published 3 years after the priority date of this application, it discussed several studies that involve molecular analysis to predict the classification between the 4 pulmonary NET. Hofsli teaches that one research group found that CPE has been found as a

good prognosis marker, which is expressed in a variety of NE cells and tumors including pituitary tumors, and it can also discriminate endocrine pancreas tumors and pheochromocytomas (see page 174, 1st col., 3rd and 4th paragraph). Hofsli also teaches that GGH expression is correlated with poor prognosis. However, these two potential markers have not been verified by other research groups. In conclusion, Hofsli states that although large scale gene expression analysis undoubtly have given interesting new hypothesis concerning genes thought to play a role in the context of tumor biology, cross-platform comparisons of gene expression studies have been difficult, and when done, have demonstrated considerable variation in gene expression results (page 175, 2nd col., 1st paragraph).

At the time of filing, the prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Kroese et al (Genetics in Medicine 6(6) :475-480, 2004) teach

genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional prior art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 18(24):20, 2004) teaches that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 3, 2nd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 3, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods, should be included in the gene association studies (e.g. page 4, 2nd paragraph).

Amount of experimentation required to make and use the claimed invention:

The claimed invention is drawn to a microarray comprising a solid support and a sufficient number of genes, or polynucleotide fragments or RNA transcripts thereof, that are differentially expressed in a small cell lung cancer cell (SCLC), a large cell neuroendocrine carcinoma neuroendocrine tumor cell (LCNEC), a typical carcinoid neuroendocrine tumor cell (TC) or an atypical carcinoid neuroendocrine tumor cell (AC), relative to a normal or a cell belong to a different neuroendocrine tumor cell type, to permit said microarray to distinguish a neuroendocrine tumor cell, and wherein said genes, or polynucleotide fragments or RNA transcripts thereof consists of CPE and GGH, or a polynucleotide fragment or RNA transcript thereof. As discussed above, the teaching of the specification fails to provide guidance with regard to how to distinguish between all types of NETs based on the expression of CPE and GGH at mRNA level. Although the immuno staining of CPE and GGH protein in SCLC, LCNEC, TC and AC samples indicates CPE is overexpressed in TC and AC, and GGH is overexpressed in LCNEC and SCLC, whether it can be used as a marker to distinguished between all types of NET is unpredictable because 1) they do not distinguish between TC and AC, LCNEC and SCLC; 2) the specification indicates that data from AC and LCNEC is not statistically significant. The issue is complicated further by lack of correlation of GGH protein and mRNA expression in SCLC samples. The teaching in the prior art does not enabled the claimed invention because the prior art recognizes that classifying tumor based on gene profiling using microarray is unpredictable based on limited study and small sample size. As such, the skilled artisan would need to engage undue experimentation to use the invention as claimed. Therefore, the claimed invention is not enabled by the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 28 and 32, the recitation of "said genes...of said microarray further includes one or more genes selected from the group..." renders the claim indefinite because claim 20 uses the word "consist" which means the microarray only consists the two recited genes, no other gene(s) is present on the array. Therefore, when additional genes are recited, the metes and bounds of the claim cannot be established.

Claim Objections

Claims 21-27 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not further limit claim 20 because they are all drawn to a microarray that consists CPE and GGH genes, polynucleotide fragments and RNA transcripts.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

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/Celine X Qian /
Primary Examiner, Art Unit 1636